

found in originally-filed claim 22 and in the specification at p. 16, lines 24-31; p. 16, line 33 to p. 17, line 6.

II. Information Disclosure Statement

The Examiner returned the PTO 1449 forms Applicants filed on February 13, 2001. However, the Examiner did not initial several abstracts listed on pages 4 and 5 of the 1449 form, apparently because no date was listed on the 1449 form for these references. However, the publication date is listed on the face of each abstract and on each patent application. Applicants respectfully request that the Examiner initial and return the aforementioned PTO 1449 form to Applicants.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 10 and 17 under 35 U.S.C. § 112, first paragraph because, according to the Examiner, these composition claims do not recite an intended use. The Examiner argues that these claims are unsupported because the claims read on all uses.

Applicants respectfully traverse this rejection because there is no statutory or judicial requirement that composition claims recite a use within the claim. The specification indicates the utility for the claimed inventions, *inter alia*, in the treatment of cardiovascular disorders such as endothelial dysfunction, high blood pressure, etc. Specification at p. 16, line 31 to p. 17, line 6. However, with the sole purpose of expediting prosecution, Applicants have cancelled claims 10 and 17. Therefore, the Examiner's rejection is now moot, and Applicants respectfully request that this rejection be withdrawn.

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IV. Rejections under 35 U.S.C. § 112, second paragraphs

The Examiner rejected claim 8 under 35 U.S.C. § 112, second paragraph as being indefinite in its recitation of a "suitable reagent." Applicants have dealt with this rejection by amendment. In order to use consistent language throughout the claims, Applicants have also amended claim 15 in a similar manner. Accordingly, Applicants respectfully request that this rejection be withdrawn.

V. Rejections under 35 U.S.C. § 112, first and second paragraphs

The Examiner rejected claims 1, 2, and 22 under 35 U.S.C. § 112, first and second paragraphs. The Examiner argues that the words "contain" or "contains" present in the definitions of the radicals R¹, R², R⁵, R⁶, and heteroaryl are open terms.

Applicants respectfully disagree with the Examiner's position. However, with the sole purpose of expediting prosecution, claims 1, 2, and 22 have been amended, eliminating the words "contain" or "contains" and maintaining the originally intended scope. Accordingly, the Examiner's rejection is now moot, and Applicants respectfully request that this rejection be withdrawn.

To the extent that the Examiner is rejecting claims 1, 2, and 22 because their scope encompass heterocyclic rings with adjacent O-S, O-O, or S-S heteroatoms, Applicants continue to traverse this rejection for the reasons of record, which the Examiner has not contested. See, e.g., Response and Amendment filed on June 10, 2002. The skilled artisan would be able to recognize any possible unstable heterocycle rings and would not attempt to prepare them. Accordingly, the claims do not run afoul of the enablement requirement.

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Also with respect to claim 22, the Examiner argues that a single compound cannot be expected to treat all cardio vascular disorders, irrespective of the cause. Applicants have amended claim 22, to clarify that this claim covers the treatment of cardio vascular disorders associated with reduced cGMP levels (i.e., a disturbance in cGMP balance) addressing the Examiner's concerns. Support for this amendment can be found on page 16, lines 24-31. Examples of disorders treated by the compounds of the invention are disclosed in the specification, e.g., at p. 16, line 33 to p. 17, line 6. Accordingly, Applicants respectfully request that this rejection be withdrawn.

VI. Rejections under 35 U.S.C. § 112, fourth paragraph

The Examiner rejected claim 15 as depending improperly from claim 5. Applicants have amended claim 15 explicitly disclosing formulas IV and VI. Accordingly, Applicants respectfully request that this rejection be withdrawn.

VII. Objections under the Utility Guidelines

The Examiner objected to claims 11 and 12 for not being acceptable utility expressions. Applicants respectfully traverse.

Foremost, Applicants believe this objection is directed only to claim 11 because claim 12 is drawn to treating the specifically mentioned medical conditions, which are clearly useful.

With respect to claim 11, activation of soluble guanylate cyclase is linked to a substantial and credible utility. For example, one embodiment of Applicants' invention indicates that the compounds of the invention "bring about strong guanylate cyclase activation, on account of which they are suitable for the therapy and prophylaxis of illnesses associated with a low cGMP level." Specification at p. 3, line 36 to p. 4, line 2.

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The specification provides various examples of such illnesses, such as endothelial, dysfunction, atherosclerosis, high blood pressure, etc. Specification at p. 16, line 33 to p. 17, line 6. Therefore, claim 11 is drawn to an acceptable utility, and Applicants respectfully request that this objection be withdrawn.

VIII. Rejections under 35 U.S.C. § 103

The Examiner rejected claim 1 under 35 U.S.C. §103, as being unpatentable over the compounds removed by the proviso at the end of claim 1. The Examiner cites *In re Nomiya*, as supporting this rejection. *In re Nomiya*, 509 F.2d 566 (C.C.P.A. 1975). Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner's interpretation of *In re Nomiya* for the reasons of record. The Examiner's position seems to be that the full scope of the proviso in claim 1 is in the prior art. Nonetheless, Applicants remind the Examiner that in the response filed January 16, 2002, Applicants broadened the proviso in claim 1 in reply to an obviousness rejection of this claim in view of *Chokai* (European Patent Application EP 0 555 478). Accordingly, the proviso in claim 1 already disclaims any compounds allegedly obvious in light of the prior art. Therefore, none of the compounds disclosed in the prior art (*i.e.*, *Chokai*) render the subject matter of the present claims unpatentable. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request the examination of this application and the timely allowance of the pending claims.

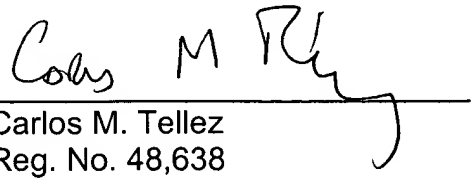
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If there is any fee due in connection with the filing of this Preliminary
Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 
Carlos M. Tellez
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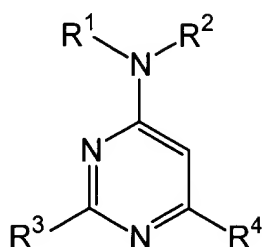
Dated: December 23, 2002

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Appendix to Response and Amendment dated December 20, 2002

1. A compound of the formula I,



in which

R¹ is (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents chosen from hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m⁻, R⁵R⁶N and aryl; (C₃-C₉)-cycloalkyl, which can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; or a radical of a 5-membered to 7-membered saturated heterocyclic ring ~~that contains~~ with one or two identical or different hetero ring members chosen from O, NR⁷ and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl and aryl-(C₁-C₄)-alkyl-;

and

R² is hydrogen, (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents chosen from hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m⁻, R⁵R⁶N and aryl; (C₃-C₉)-cycloalkyl, which can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; or the radical of a 5-membered to 7-membered saturated heterocyclic ring ~~that contains~~ with one or two identical or

different hetero ring members chosen from O, NR^7 and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl and aryl-(C₁-C₄)-alkyl; or

$\text{R}^1\text{R}^2\text{N}$ is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated heterocyclic ring that optionally with, in addition to the nitrogen atom carrying the radicals R^1 and R^2 , ~~can contain~~ a further hetero ring member chosen from O, NR^7 and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl, (C₁-C₄)-alkoxy, $\text{R}^8\text{R}^9\text{N}$, hydroxycarbonyl, (C₁-C₄)-alkoxycarbonyl and $\text{R}^8\text{R}^9\text{N-CO-}$;

R^3 is phenyl, which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF_3 , NO_2 , OH, -O-(C₁-C₄)-alkyl, -O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH_2 , -NH-(C₁-C₄)-alkyl, $\text{N}((\text{C}_1\text{-C}_4)\text{-alkyl})_2$, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, -CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

R^4 is (C₂-C₅)-alkyl, trifluoromethyl or phenyl, which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF_3 , NO_2 , OH, -O-(C₁-C₄)-alkyl, -O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH_2 , -NH-(C₁-C₄)-alkyl, $\text{N}((\text{C}_1\text{-C}_4)\text{-alkyl})_2$, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, -CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

R^5 and R^6 are identical or different radicals chosen from hydrogen and (C₁-C₄)-alkyl; or the group $\text{R}^5\text{R}^6\text{N}$ is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated or unsaturated heterocyclic ring

that optionally with, in addition to the nitrogen atom carrying the radicals R^5 and R^6 , ~~can additionally contain as~~ a further hetero ring member chosen from an oxygen atom, a group $S(O)_m$ ~~or and~~ a nitrogen atom and that can carry on ring carbon atoms one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino and that can carry on a ring nitrogen atom a radical R^7 ;

R^7 is hydrogen, (C₁-C₄)-alkyl, aryl-(C₁-C₄)-alkyl-, hydroxy-(C₁-C₄)-alkyl, hydroxycarbonyl-(C₁-C₄)-alkyl-, ((C₁-C₄)-alkoxycarbonyl)-(C₁-C₄)-alkyl, $R^8R^9N-CO-(C_1-C_4)-alkyl-$, $R^{10}-SO_2-$ or aryl; where R^7 , if this group is present on a piperazino radical representing R^1R^2N , cannot be carbocyclic aryl or carbocyclic aryl-(C¹-C⁴)-alkyl;

R^8 and R^9 are identical or different radicals chosen from hydrogen and (C₁-C₄)-alkyl;

R^{10} is (C₁-C₄)-alkyl, aryl or R^8R^9N ;

aryl is phenyl, naphthyl or heteroaryl, all of which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF₃, NO₂, OH, -O-(C₁-C₄)-alkyl, O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH₂, -NH-(C₁-C₄)-alkyl, -N((C₁-C₄)-alkyl)₂, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

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heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which ~~contains~~ with one or more identical or different ring heteroatoms chosen from N, O and S;

m is 0, 1 or 2;

or a stereoisomeric form of a compound of formula I,

or a mixture of stereoisomeric forms of compounds of formula I in all ratios,

or a physiologically tolerable salt of a compound of formula I,

or a physiologically tolerable salt of a stereoisomeric form of a compound of formula I;

compounds of the formula I being excluded in which, simultaneously, R⁴ is ethyl, tert-butyl, or trifluoromethyl; R³ is phenyl, which can be substituted by one or two identical or different substituents chosen from halogen, OH, -O-R¹¹ and CF₃, R¹R²N is R¹¹ -NH-, (R¹¹)₂N- or R¹²R¹³N-(CH₂)_p-NH-; p is 2 or 3; R¹¹ is saturated unsubstituted (C₁-C₄)-alkyl; and R¹² and R¹³ are identical or different radicals chosen from hydrogen and R¹¹ or the group R¹²R¹³N is a radical, bonded via a ring nitrogen atom, of a 5-membered or 6-membered saturated heterocyclic ring ~~that~~ optionally with, in addition to the nitrogen atom carrying the radicals R¹² and R¹³, ~~can additionally contain as~~ a further hetero ring member chosen from an oxygen atom, a sulfur atom ~~or~~ and a nitrogen atom and that can be substituted by an aryl substituted by one or two identical or different substituents chosen from halogen, OH, -O-R¹¹, and CF₃.

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2. A compound of claim 1, in which

R¹ is (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents, chosen from, hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m-, R⁵R⁶N and aryl; or is (C₃-C₉)-cycloalkyl, which can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; and

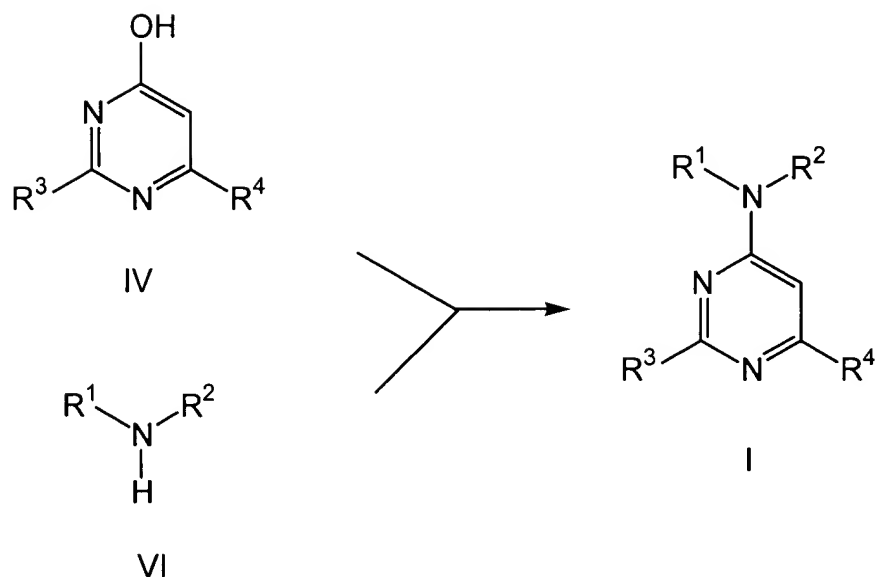
R² is hydrogen, (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents chosen from hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m-, R⁵R⁶N and aryl; or is (C₃-C₉)-cycloalkyl, which can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; or

R¹R²N is a radical, bonded via a ring nitrogen atom of a 5-membered, 6-membered or 7-membered saturated heterocyclic ring that optionally with, in addition to the nitrogen atom carrying the radicals R¹ and R², can additionally contain as a further hetero ring member chosen from an oxygen atom, a group S(O)_m or and a nitrogen atom carrying a radical R⁷ and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl, (C₁-C₄)-alkoxy, R⁸R⁹N, hydroxycarbonyl, (C₁-C₄)-alkoxycarbonyl and R⁸R⁹N-CO.

8. A process for the preparation of at least one compound of claim 1, which comprises activating a 4-hydroxypyrimidine of the formula IV and then reacting it with an amine of a formula VI to produce a compound of formula I,

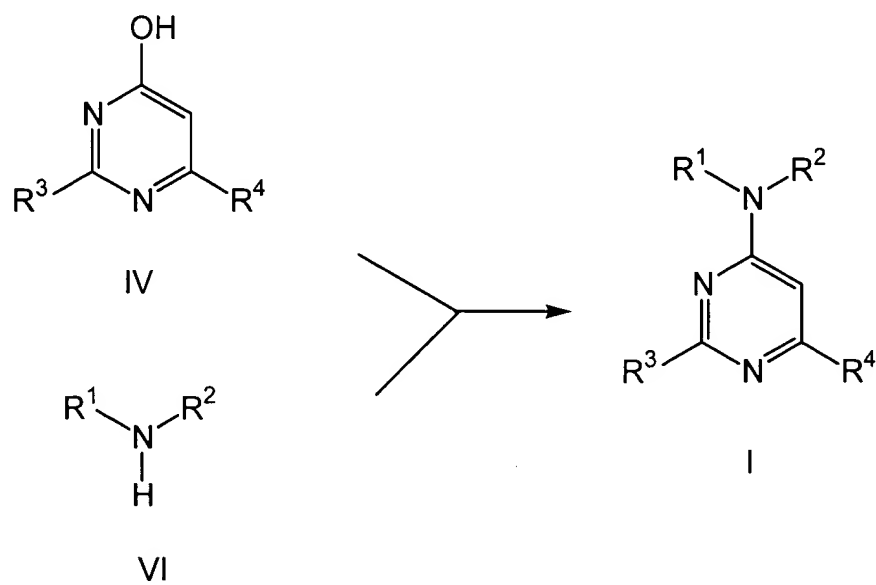
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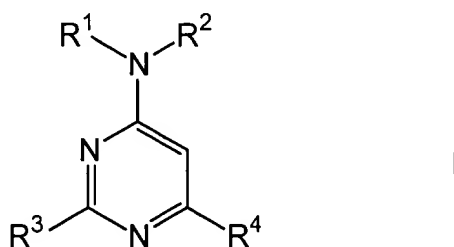
and optionally ~~reacting~~ converting a compound of formula I ~~with a suitable reagent to form~~ into a pharmaceutically acceptable salt.

15. A process for the preparation of at least one compound of claim 5, which comprises activating a 4-hydroxypyrimidine of the formula IV and then reacting it with an amine of a formula VI;



and optionally ~~reacting~~converting the resulting product ~~with a suitable reagent to form into~~ a pharmaceutically acceptable salt.

22. A method of treating a cardiovascular disorder associated with reduced cGMP levels, comprising administering to a patient in need thereof an effective amount of at least one compound of formula I,



in which

R¹ is (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents chosen from hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m-, R⁵R⁶N and aryl; (C₃-C₉)-cycloalkyl, which can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; or a radical of a 5-membered to 7-membered saturated heterocyclic ring that contains with one or two identical or different hetero ring members chosen from O, NR⁷ and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl and aryl-(C₁-C₄)-alkyl-;

and

R² is hydrogen, (C₁-C₈)-alkyl, which can be substituted by one or more identical or different substituents chosen from hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl-S(O)_m-, R⁵R⁶N and aryl; (C₃-C₉)-cycloalkyl, which can be substituted

by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino; or the radical of a 5-membered to 7-membered saturated heterocyclic ring ~~that contains~~with one or two identical or different hetero ring members chosen from O, NR⁷ and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl and aryl-(C₁-C₄)-alkyl-; or

R¹R²N is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated heterocyclic ring ~~that~~optionally with, in addition to the nitrogen atom carrying the radicals R¹ and R², ~~can contain~~ a further hetero ring member chosen from O, NR⁷ and S(O)_m and that can be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl, (C₁-C₄)-alkoxy, R⁸R⁹N, hydroxycarbonyl, (C₁-C₄)-alkoxycarbonyl and R⁸R⁹N-CO-;

R³ is phenyl, which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF₃, NO₂, OH, -O-(C₁-C₄)-alkyl, -O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH₂, -NH-(C₁-C₄)-alkyl, N((C₁-C₄)-alkyl)₂, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, -CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

R⁴ is (C₂-C₅)-alkyl, trifluoromethyl or phenyl, which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF₃, NO₂, OH, -O-(C₁-C₄)-alkyl, -O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH₂, -NH-(C₁-C₄)-alkyl, N((C₁-C₄)-alkyl)₂, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, -CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

R^5 and R^6 are identical or different radicals chosen from hydrogen and (C₁-C₄)-alkyl; or the group R^5R^6N is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated or unsaturated heterocyclic ring that optionally with, in addition to the nitrogen atom carrying the radicals R^5 and R^6 , ~~can additionally contain as~~ a further hetero ring member chosen from an oxygen atom, a group S(O)_m ~~or and~~ a nitrogen atom and that can carry on ring carbon atoms one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxyl and amino and that can carry on a ring nitrogen atom a radical R^7 ;

R^7 is hydrogen, (C₁-C₄)-alkyl, aryl-(C₁-C₄)-alkyl-, hydroxy-(C₁-C₄)-alkyl, hydroxycarbonyl-(C₁-C₄)-alkyl-, ((C₁-C₄)-alkoxycarbonyl)-(C₁-C₄)-alkyl, R^8R^9N -CO-(C₁-C₄)-alkyl-, R^{10} -SO₂- or aryl; where R^7 , if this group is present on a piperazino radical representing R^1R^2N , cannot be carbocyclic aryl or carbocyclic aryl-(C¹-C⁴)-alkyl;

R^8 and R^9 are identical or different radicals chosen from hydrogen and (C₁-C₄)-alkyl;

R^{10} is (C₁-C₄)-alkyl, aryl or R^8R^9N ;

aryl is phenyl, naphthyl or heteroaryl, all of which can be substituted by one or more identical or different substituents chosen from halogen, (C₁-C₄)-alkyl, phenyl, CF₃, NO₂, OH, -O-(C₁-C₄)-alkyl, O-(C₂-C₄)-alkyl-O-(C₁-C₄)-alkyl, (C₁-C₂)-alkylenedioxy, NH₂, -NH-(C₁-C₄)-alkyl, -N((C₁-C₄)-alkyl)₂, -NH-CHO, -NH-CO-(C₁-C₄)-alkyl, -CN, CO-NH₂, -CO-NH-(C₁-C₄)-alkyl, -CO-

N((C₁-C₄)-alkyl)₂, -CO-OH, -CO-O-(C₁-C₄)-alkyl, -CHO and -CO-(C₁-C₄)-alkyl;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which ~~contains~~ with one or more identical or different ring heteroatoms chosen from N, O and S;

m is 0, 1 or 2;

or a stereoisomeric form of a compound of formula I,

or a mixture of stereoisomeric forms of compounds of formula I in all ratios,

or a physiologically tolerable salt of a compound of formula I,

or a physiologically tolerable salt of a stereoisomeric form of a compound of formula I.

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